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Full Paper

Synthesis of Analogues of Thyroid Hormones: Nuclear Receptor Modulators

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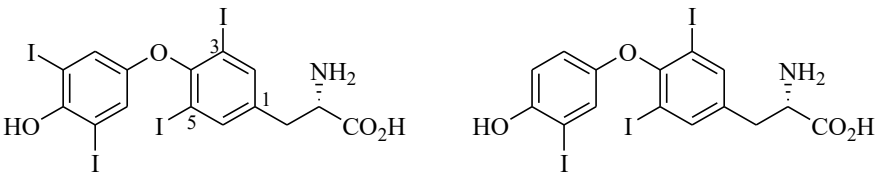
Abstract: Thyroid hormones are essential for the development and differentiation of all cells of the human body. This work reports the synthesis of some synthetic structural analogues of thyroid hormones, which may be modulators of the thyroid hormone receptor. The known compounds **GC-1** (Sobetirome) and **CG-24** were successfully prepared and two novel analogous molecules were also synthesized by a new and efficient synthetic methodology.

Keywords: thyroid hormones; nuclear receptor; ligands; synthesis

1. INTRODUCTION

Thyroid hormones (THs) participate in differentiation, growth, and metabolism in several tissues of vertebrates. The thyroid gland mainly releases the hormone thyroxine (**T4**), but it also secretes a smaller amount of 3,5,3'-triiodothyronine (**T3**) (compounds **1** and **2** shown in Figure 1, respectively). **T3** originates mostly from **T4** deiodination in peripheral tissues, and it is the major active form of THs in TH-responsive tissues. Thyroid hormone receptors (TRs), members of the nuclear receptor family, mediate the actions of **T3**. These receptors are transcription factors that bind to DNA via specific sequences of target genes [1, 2].



T4 (1) **T3 (2)**

Figure 1. Chemical structures of the thyroid hormones **T4** (**1**) and **T3** (**2**).

In general, nuclear receptors (NRs) regulate a wide range of physiologic and developmental processes. Virtually all the NRs that can identify ligands constitute well-characterized targets for the development of drugs to treat myriad diseases including cancer, diabetes, atherosclerosis, inflammation, and endocrine/reproductive disorders [3].

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The pharmacological effects of THs could help to treat several disorders, but they generally cause both useful and adverse effects. Their potentially favorable features include weight reduction to combat obesity [4], cholesterol lowering to treat hyperlipidemia [5-7], amelioration of depression and stimulation of bone formation in osteoporosis [8, 9]. Manifestations of hyperthyroidism and cardiovascular toxicity have limited prior attempts to employ thyroid hormones in the pharmacological treatment of these conditions. Therefore, the development of TR ligands that are more selective for the isoforms of receptor α (TRα) or β (TRβ) could lead to specific and safer therapies for these disorders [10].

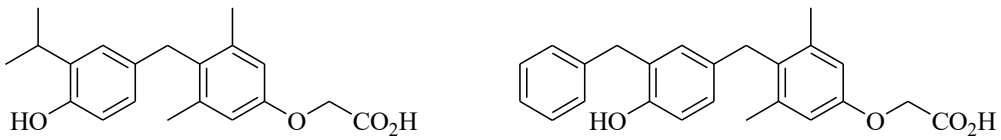
Several lines of evidence have demonstrated that the isoform-selective agonist of receptor β reduces cholesterol with minimum tachycardia [11]. Other observations have suggested that the α-isoform of receptors stimulates the cardiac side effects [12].

The creation of a synthetic analogue of $\mathbf{T_3}$ (**2**), called **GC-1** (**3**) and also known as sobetirome or QRX-431, revolutionized the design of TR ligands. Figure 2 depicts the structure of **GC-1** (**3**), which is a halogen-free compound. Scanlan et al. designed and synthesized **GC-1** (**3**) with an overall yield of 22%. These authors also showed that this compound has high affinity for the TRβ isoform [13-15], the isoform that predominates in the liver and accounts for the lipid-lowering activities of THs. The exact mechanisms of liver selectivity remain unclear [3].

Researchers have also tested **GC-1** (**3**) in cholesterol-fed rats as well as in hypothyroid mice and primates, to elucidate how it affects the levels of cholesterol and triglycerides and the cardiac activity. In three model systems, **GC-1** (**3**) lowered the levels of circulating cholesterol (90% in rats and 35-40% in cynomolgus monkeys at the highest applied dose) to concentrations that did not significantly impact the heart rate [16].

Scientists have designed another potentially pharmacologically useful compound – **GC-24** (**4**), a second-generation thyromimetic molecule that differs from **GC-1** (**3**) in the 3' position of the second aromatic ring, where a benzyl group substitutes the isopropyl group (Figure 2). This replacement improves TRβ selectivity by a factor of 40-60 while maintaining the binding affinity and the receptor function of the molecule [17]. **GC-24** (**4**) partially improves metabolic control in high fat-fed rats [18]. Unlike $\mathbf{T_3}$ (**2**), **GC-24** (**4**) does not alter the composition of the skeletal muscle fiber [19].

The useful properties of this class of compounds justify additional investigation into their properties, which could aid the treatment of lipid disorders [20]. TH mimics display selective actions and undergo selective uptake by the liver tissue as compared with the heart, bone, and muscle tissue. Such analogues could serve as powerful new tools to address two of the largest medical problems in developed countries, atherosclerosis and obesity [21].



GC-1 (3) **GC-24 (4)**

Figure 2. Chemical structures of two TR ligands, G**C-1** (**3**) and **GC-24** (**4**).

Recently, a study has shown that integrins (structural proteins of the plasma membrane) have a panel of previously unappreciated small molecule receptor sites for TH and hormone analogues, dihydrotestosterone, and resveratrol, a polyphenol that has certain estrogen-like features. Occupancy of the receptor by a TH analogue modulated the expression of a number of cancer cell survival pathway genes in an up- or down-regulated pattern coherent with cell death induction. The small molecule also regulated the activity of five vascular growth factor receptors and/or their ligands, providing control of angiogenesis [22].

In this paper, we report a new synthetic route to prepare the pharmacologically important ligands **GC-1** (**3**) and **GC-24** (**4**), as outlined in Scheme 1. We successfully synthesized these two ligands and synthesized two novel ligands (compounds **19** and **20** shown in Scheme 2). These new molecules could be potentially useful to treat several human disorders, because their design promoted functional changes in position 1 of the structural skeleton of TH analogues.

The compounds **GC-1** (**3**) and **GC-24** (**4**) have

been submitted to binding studies with human transthyretin (TTR), a tetrameric β-sheet-rich transporter protein that directly participates in human amyloid diseases. We tested and characterized the interaction of **GC-1** (**3**) and **GC-24** (**4**) with TTR; we also performed *in vitro* TTR acid-mediated aggregation assays, isothermal titration calorimetry (ITC) and X-ray crystallography experiments. The results of this study are already published [23].

2. MATERIAL AND METHODS

The solvents and other common reagents were commercially available. TLC was performed on precoated silica gel 60 F_{254} (0.25 mm thick, Merck). Column chromatography separation was performed with silica gel 60 (70-230 mesh, Merck). All ^{1}H and ^{13}C NMR spectra were recorded at 500 and 125 MHz, respectively, on a Bruker DPX-500 instrument; chloroform-*d* ($CDCl_3$) or methanol-d_4 (CD_3OD) was used as solvent; chemical shifts are in ppm downfield from a tetramethylsilane internal standard. IR spectra were recorded on a Perkin Elmer Spectrum RX IFTIR System, in KBr pellets or plates. Mass spectra were determined at an ionizing voltage of 70 eV, using an HP 5988-A or a Shimadzu QP 2010 spectrometer. The high-resolution (HR) ESI-MS analyses were carried out on a hybrid quadrupole time-of-flight (Q-TOF) mass spectrometer (micrOTOF, Bruker Daltonics, Billerica, MA, USA) fitted with an ESI source operating in the positive ion mode. Samples were directly infused into the ionization source at a flow rate of 10 μL/min. The source block and desolvation temperature was 150 ºC. The use of sodium trifluoroacetate as the mass standard provided accurate masses after each analysis, and the formulae proposed for each ion (protonated and cationized molecules) were based on errors, which were less than 5 ppm from the calculated mass.

2-Benzyl-4-bromophenol (6) and 4-bromo-2-isopropyl-phenol (6a)

2-Hydroxydiphenylmethane (**5**) (2.03 g, 11.0 mmol) or 2-isopropylphenol (**5a**) (1.50 g, 11.0 mmol) dissolved in dry dichloromethane (20 mL) was added to a dry three-neck round-bottom flask fitted with a drying tube. The solution was cooled to 0 ºC, and bromine (1.76 g, 11.0 mmol, 0.57 mL) was added dropwise at 0 ºC. The reaction mixture was stirred for 1 h at 0 ºC. After this period, the mixture was treated with water and $NaHCO_3$ saturated solution, and extracted with dichloromethane. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. After concentration of the organic phase under reduced pressure, the crude residue was purified by silica-gel column chromatography (hexanes-ethyl acetate, 9:1), to give the brominated compound **6** (2.52 g, 9.58 mmol, 87%) as a slightly yellow solid (mp 57–59 ºC) or **6a** (2.13 g, 9.90 mmol, 90%) as a red oil.

Compound 6: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.84 (s, 2 H, CH_2, Bn), 4.90 (br s, 1 H, OH), 6.48 (d, 1 H, J = 8.5 Hz, H-5), 7.09–7.25 (m, 7 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 35.9, 112.9, 117.3, 126.5, 128.5, 128.6, 129.4, 130.3, 133.3, 139.0, 152.6. IR (KBr, cm^{-1}): 3533, 1494–1602, 1270, 1044. MS *m/z* (%) 264 (96) $[M+2]^+$, 184 (56), 166 (45), 77 (61), 50 (100).

Compound 6a: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (d, 6 H, J = 7.0 Hz, CH_3, *i*-Pr), 3.21 (hept, 1 H, J = 7.0 Hz, CH, *i*-Pr), 5.50 (br s, 1 H, OH), 6.61 (d, 1 H, J = 8.6 Hz, H-5), 7.11 (dd, 1 H, J = 2.4 Hz, J = 8.6 Hz, H-6), 7.28 (d, 1 H, J = 2.4 Hz, H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.5, 27.0, 113.0, 117.0, 129.5, 137.0, 152.0. IR (KBr, cm^{-1}): 3425, 1500–1600, 1253, 1097. MS *m/z* (%) 216 (45) $[M+2]^+$, 201 (91), 120 (100), 102 (39), 91 (77), 62 (86).

(2-Benzyl-4-bromophenoxy)triisopropylsilane (7) and (4-bromo-2-isopropyl-phenoxy)triisopropylsilane (7a)

A solution of compound **6** (1.05 g, 4.00 mmol) or **6a** (0.860 g, 4.00 mmol), imidazole (0.600 g, 8.80 mmol), and triisopropylsilyl chloride (0.850 g, 4.40 mmol, 0.93 mL) in dry dichloromethane (18 mL) was stirred under dry nitrogen atmosphere, at room temperature, for 1 h. After this period, the reaction mixture was diluted with dichloromethane, washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude residue was purified by silica-gel column chromatography (hexanes/ethyl acetate, 9:1), to afford compound **7** (1.27 g, 3.03 mmol, 76%) as a slightly yellow oil or **7a** (1.17 g, 3.15 mmol, 79%) as a white solid (mp 50–51.5 ºC).

Compound 7**:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (d, 18 H, J = 7.5 Hz, CH_3, TiPS), 1.25 (hept, 3 H, J = 7.5 Hz, CH, TiPS), 3.95 (s, 2 H, CH_2, Bn), 6.69 (d, 1 H, J = 8.5 Hz, H-5), 7.09 (d, 1 H, J = 2.6 Hz, H-2), 7.15 (m, 3 H, CH, Bn), 7.16 (dd, 1 H, J = 2.6 Hz, J = 8.5 Hz, H-6), 7.25 (m, 2 H, CH, Bn). ^{13}C NMR (125

MHz, $CDCl_3$): δ 13.1, 18.0, 36.0, 113.0, 119.4, 126.0, 128.4, 128.9, 129.9, 133.4, 133.6, 140.0, 153.1. IR (KBr, cm^{-1}): 1587, 1486, 1274, 1116, 846. MS *m/z* (%) 420 (14) $[M+2]^+$, 377 (100), 349 (12), 305 (15), 91 (34).

Compound 7a: ^1H NMR (500 MHz, $CDCl_3$): δ 1.11 (d, 18 H, *J* = 7.4 Hz, CH_3, TiPS), 1.19 (d, 6 H, *J* = 7.0 Hz, CH_3, *i*-Pr), 1.30 (m, 3 H, *J* = 7.4 Hz, CH, TiPS), 3.30 (m, 1 H, *J* = 7.0 Hz, CH, *i*-Pr), 6.64 (d, 1 H, *J* = 8.4 Hz, H-5), 7.11 (dd, 1 H, *J* = 8.4 Hz, *J* = 2.6 Hz, H-6), 7.27 (d, 1 H, *J* = 2.6 Hz, H-2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.1, 18.0, 22.6, 26.9, 113.2, 119.4, 129.0, 129.3, 141.0, 152.3. IR (KBr, cm^{-1}): 1485, 1279, 1191, 880. MS *m/z* (%) 372 (22) $[M+2]^+$, 329 (57), 58 (100).

5-(Benzyloxy)-2-bromo-1,3-dimethylbenzene (9)

Potassium carbonate (2.76 g, 20.0 mmol), tetra-*n*-butylammonium fluoride (0.300 mmol, 1.0 mol/L in THF), and benzyl bromide (1.86 g, 10.9 mmol, 1.30 mL) were added to a solution of 4-bromo-3,5-dimethylphenol (**8**) (2.00 g, 9.95 mmol) in acetone (20 mL). The yellow reaction mixture was heated to reflux and stirred under dry nitrogen atmosphere. After 2 h, the starting material was completely consumed. Then, the reaction mixture was cooled, filtered, and concentrated under reduced pressure. Compound **9** was obtained in the pure form without any purification (2.86 g, 9.83 mmol, 99%), as a white solid (mp 49–50 °C).

^1H NMR (500 MHz, $CDCl_3$): δ 2.36 (s, 6 H, CH_3), 5.01 (s, 2 H, CH_2, Bn), 6.71 (s, 2 H), 7.29–7.43 (m, 5 H, CH, Bn). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.0, 70.1, 114.8, 118.5, 127.4, 127.9, 128.6, 136.9, 139.2, 157.3. IR (KBr, cm^{-1}): 1464–1582, 1165, 1018, 855. MS *m/z* (%) 292 (7) $[M+2]^+$, 91 (100), 64 (20).

4-(Benzyloxy)-2,6-dimethylbenzaldehyde (10)

n-Butyllithium 1.6 mol/L (8.60 mL, 13.7 mmol) was added to a solution of compound **9** (2.00 g, 6.87 mmol) in anhydrous tetrahydrofuran (35 mL) under nitrogen atmosphere at −78 °C, which was followed by addition of dimethylformamide (1.00 g, 13.7 mmol, 1.06 mL). Next, the reaction mixture was stirred for 2.5 h at −78 °C. After this period, the temperature was elevated to room temperature, and the reaction mixture was diluted with ether and acidified with HCl 6 mol/L. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica-gel column chromatography (hexanes-ethyl acetate, 9:1), to yield compound **10** (1.29 g, 5.37 mmol, 78%) as a white solid (mp 59–60 °C).

^1H NMR (500 MHz, $CDCl_3$): δ 2.60 (s, 6 H, CH_3), 5.08 (s, 2 H, OCH_2, Bn), 6.65 (s, 2 H), 7.29–7.45 (m, 5 H, CH, Bn), 10.45 (s, 1 H, CHO). ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.9, 69.9, 115.7, 127.4, 128.1, 128.6, 136.3, 144.3, 161.9, 191.4. IR (KBr, cm^{-1}): 2870, 1682, 1454–1598, 1148. MS *m/z* (%) 240 (14), 91 (100), 64 (22).

{[3-Benzyl-4-(triisopropylsilyloxy)phenyl] [4-(benzyl-oxy)-2,6-dimethylphenyl]} methanol (11) and {[4-(benzyloxy)-2,6-dimethylphenyl][3-isopropyl-4-(triisopropyl-silyloxy)phenyl]} methanol (11a)

n-Butyllithium 1.6 mol/L in hexane (0.94 mL, 1.5 mmol) was added to a solution of compound **7** (0.419 g, 1.0 mmol) or **7a** (0.371 g, 1.0 mmol) in anhydrous tetrahydrofuran (about 10 mL) under nitrogen atmosphere at −78 °C. After brief agitation, a solution of aldehyde **10** (0.240 g, 1.0 mmol) in anhydrous tetrahydrofuran (about 5.0 mL) was added. The reaction mixture was stirred for 2.5 h at −78 °C and for 8 h at room temperature. After that, the reaction mixture was diluted with ether and washed with water and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude compounds **11** or **11a**, which were used in the next step without further purification.

***Compound 11*:** ^1H NMR (500 MHz, $CDCl_3$): δ 1.04 (d, 18 H, *J* = 7.5 Hz, CH_3, TiPS), 1.24 (m, 3 H, CH, TiPS), 2.18 (s, 6 H, CH_3), 3.97 (m, 2 H, CH_2, Bn), 4.99 (s, 2 H, OCH_2, Bn), 6.14 (s, 1 H, H-7), 6.61 (s, 2 H, H-2, H-6), 6.73 (d, 1 H, *J* = 8.5 Hz, H-10), 6.87 (dd, 1 H, *J* = 1.8 Hz, *J* = 8.5 Hz, H-9), 7.03 (d, 1 H, *J* = 1.8 Hz, H-13), 7.09–7.22 (m, 5 H), 7.27–7.42 (m, 5 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 17.9, 20.8, 36.2, 69.6, 70.5, 115.1, 117.5, 124.4, 125.5, 127.3, 127.8, 128.0, 128.3, 128.4, 128.6, 130.4, 132.4, 135.3, 137.2, 138.6, 141.1, 152.4, 157.6.

***Compound 11a*:** ^1H NMR (500 MHz, $CDCl_3$): δ 1.09 (d, 18 H, *J* = 7.5 Hz, CH_3, TiPS), 1.15 (d, 6 H, *J* = 6.8 Hz, CH_3, *i*-Pr), 1.27 (m, 3 H, CH, TiPS), 2.16 (s, 6 H, CH_3), 3.34 (hept, 1 H, *J* = 6.8 Hz, CH, *i*-Pr), 5.08 (s, 2 H, OCH_2, Bn), 6.17 (s, 1 H, H-7), 6.52 (s, 2 H, H-2, H-6), 6.63 (d, 1 H, *J* = 8.2 Hz, H-10), 6.70 (m, 1 H,

H-9), 7.19 (d, 1 H, *J* = 2.2 Hz, H-13), 7.24–7.36 (m, 5 H, CH, Bn). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.1, 18.0, 20.9, 22.7, 26.8, 69.8, 71.0, 116.3, 117.4, 123.4, 123.6, 126.0, 127.3, 128.5, 132.0, 135.2, 138.1, 138.4, 142.5, 151.7, 157.2.

4-[3-Benzyl-4-(triisopropylsilyloxy)benzyl]-3,5-dimethylphenol (12) and 4-[3-isopropyl-4-(triisopropyl-silyloxy)benzyl]-3,5-dimethylphenol (12a)

The catalyst 10% palladium on activated carbon powder (6 mg) was added to a solution of compound **11** or **11a** (~0.600 g, 1.0 mmol) in a mixture of ethanol/acetic acid (90:10 v/v) (about 5.0-8.0 mL or the necessary volume to dissolve all reactants). The suspension was stirred under hydrogen pressure (4 atm) at room temperature, in a stainless steel reactor. After 2 days, the catalyst was removed by filtration through Celite® and silica gel, and the solvent was evaporated under reduced pressure. The obtained residue was diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer was separated, dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica-gel column chromatography (hexanes-ethyl acetate, 8:2), to give compound **12** (0.303 g, 0.639 mmol, 64%, two steps) or **12a** (0.264 g, 0.620 mmol, 62%, two steps) as an oil.

***Compound 12*:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (d, 18 H, *J* = 7.5 Hz, CH_3, TiPS), 1.24 (hept, 3 H, *J* = 7.5 Hz, CH, TiPS), 2.14 (s, 6 H, CH_3), 3.81 (s, 2 H, H-7), 3.95 (s, 2 H, CH_2, Bn), 6.51 (s, 2 H, H-2, H-6), 6.60 (dd, 1 H, *J* = 1.8 Hz, *J* = 8.5 Hz, H-9), 6.66 (d, 1 H, *J* = 8.5 Hz, H-10), 6.72 (d, 1 H, *J* = 1.8 Hz, H-13), 7.11-7.26 (m, 5 H, CH, Bn). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 18.0, 20.3, 33.5, 36.2, 114.7, 117.7, 125.6, 126.0, 128.1, 128.8, 129.8, 130.5, 130.6, 132.0, 138.6, 141.1, 151.8, 153.4. IR (KBr, cm^{-1}): 3574, 1448, 1243, 1047. MS *m/z* (%) 474 (5), 383 (30), 135 (100).

***Compound 12a*:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (d, 18 H, *J* = 7.6 Hz, CH_3, TiPS), 1.15 (d, 6 H, *J* = 7.1 Hz, CH_3, *i*-Pr), 1.27 (hept, 3 H, *J* = 7.6 Hz, CH, TiPS), 2.19 (s, 6 H, CH_3), 3.32 (hept, 1 H, *J* = 7.1 Hz, CH, *i*-Pr), 3.88 (s, 2 H, H-7), 6.51 (dd, 1 H, *J* = 2.3 Hz, *J* = 8.4 Hz, H-9), 6.54 (s, 2 H, H-2, H-6), 6.60 (d, 1 H, *J* = 8.4 Hz, H-10), 6.92 (d, 1 H, *J* = 2.3 Hz, H-13). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.0, 18.0, 20.6, 22.8, 26.6, 33.8, 114.6, 117.6, 124.8, 125.8, 130.0, 131.9, 138.1, 138.7, 151.0, 153.3. IR (KBr, cm^{-1}): 3413, 1492, 1267, 1046. MS *m/z* (%) 426 (35), 383 (24), 135 (100).

[4-(4-Hydroxy-3-isopropylbenzyl)-3,5-dimethylphenoxy]acetic acid − GC-1 (3) and [4-(3-benzyl-4-hydroxybenzyl)-3,5-dimethylphenoxy] acetic acid − GC-24 (4)

Sodium hydride (60% in mineral oil, 0.625 mmol), anhydrous tetrahydrofuran (7.0 mL), and a solution of compound **12** (0.118 g, 0.250 mmol) or **12a** (0.106 g, 0.250 mmol) in anhydrous tetrahydrofuran (1.0 mL) were added to a dry three-neck round-bottom flask under nitrogen atmosphere at 0 °C, which was followed by addition of bromoacetic acid (0.0417 g, 0.300 mmol). The resulting suspension was stirred for 12 h, under reflux. After this period, the reaction mixture was acidified with HCl 6 mol/L (about 1.0 mL) and extracted with ethyl acetate. The organic layer was separated and concentrated under reduced pressure. Tetra-*n*-butyl-ammonium fluoride 1.0 mol/L in THF (1.0 mL, 1.0 mmol) was added to the obtained residue, to promote the instantaneous cleavage of the silyl group. Then, the reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was separated and concentrated under reduced pressure. The crude residue was purified with difficulty by silica-gel column chromatography (hexanes-ethyl acetate-AcOH, 59:39:2), to yield **GC-1** (**3**) (0.0500 g, 0.152 mmol, 61%, two steps) as a slightly yellow solid (mp 98–100 °C) or **GC-24** (**4**) (0.0562 g, 0.149 mmol, 60%, two steps) as a white solid (mp 153–154 °C).

***Compound 3*:** ^{1}H NMR (500 MHz, CD_3OD): δ 1.12 (d, 6 H, *J* = 7.0 Hz, CH_3, *i*-Pr), 2.16 (s, 6 H, CH_3), 3.19 (hept, 1 H, *J* = 7.0 Hz, CH, *i*-Pr), 3.85 (s, 2 H, H-7), 4.80 (s, 2 H, CH_2, acid), 6.51 (dd, 1H, *J* = 1.0 H, *J* = 8.0 Hz, H-9), 6.58 (d, 1 H, *J* = 8.0 Hz, H-10), 6.65 (s, 2 H, H-2, H-6), 6.83 (d, 1 H, *J* = 1.0 Hz, H-13). ^{13}C NMR (125 MHz, CD_3OD): δ 20.5, 23.1, 28.0, 34.5, 65.8, 115.1, 115.8, 126.3, 126.6, 131.9, 132.2, 135.8, 139.5, 153.4, 157.2, 170.6. IR (KBr, cm^{-1}): 3445, 1755, 1429, 1151, 1094. MS *m/z* (%) 270 (64), 255 (52), 227 (19), 134 (100), 91 (35).

***Compound 4*:** ^{1}H NMR (500 MHz, CD_3OD): δ 2.02 (s, 6 H, CH_3), 3.70 (s, 2 H, H-7), 3.73 (s, 2 H, CH_2, Bn), 4.48 (s, 2 H, CH_2, acid), 6.48 (m, 1 H, H-10), 6.49 (s, 2 H, H-2, H-6), 6.52 (m, 2 H, H-9, H-13), 6.97–7.03 (m, 3 H, CH, Bn), 7.06–7,11 (m, 2 H, CH,

Bn). ^{13}C NMR (125 MHz, CD_3OD): δ 20.5, 34.2, 36.6, 65.9, 115.1, 115.9, 126.6, 127.3, 128.9, 129.1, 129.8, 131.1, 132.0, 132.1, 139.4, 142.7, 154.1, 157.3, 173.0. IR (KBr, cm^{-1}): 3418, 1714, 1456, 1152, 1020. MS *m/z* (%) 376 (84), 282 (62), 208 (100), 91 (35), 73 (65).

3-Methoxy-4-(triisopropylsilyl)benzaldehyde (14)

A mixture of vanillin (**13**) (2.13 g, 14.0 mmol), imidazole (2.05 g, 30.0 mmol), and triisopropylsilyl chloride (2.36 g, 12.3 mmol, 2.60 mL) in dichloromethane (25 mL) was stirred under atmosphere of dry nitrogen at room temperature for 3 h. After this period, water and dichloromethane were added to the mixture, and the organic layer was separated and washed with water and brine, which was followed by drying over anhydrous $MgSO_4$, filtration, and evaporation. The obtained residue was purified by silica-gel column chromatography (hexanes-ethyl acetate, 8:2), to furnish compound **14** (3.11 g, 10.1 mmol, 72%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (d, 18 H, *J* = 7,6 Hz, TiPS), 1.27 (hept, 3 H, *J* = 7,6 Hz, TiPS), 3.85 (s, 3 H), 6.97 (d, 1 H, *J* = 8.0 Hz), 7.35 (dd, 1 H, *J* = 1.5 Hz, *J* = 8.0 Hz), 7.38 (d, 1 H, *J* = 1.5 Hz), 9.85 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.8, 17.6, 55.1, 110.1, 120.0, 125.7, 130.6, 151.4, 151.5, 190.3. HRMS *m/z* calcd. for $C_{17}H_{28}O_3Si^+$ $[M+H]^+$: 309.1886, found: 309.1913.

2-(4-Bromophenyl)-1,3-dioxolane (16)

A mixture of *p*-bromobenzaldehyde (**15**) (2.50 g, 13.5 mmol), ethylene glycol (0.936 g, 15.1 mmol, 8.26 mL), and *p*-toluenesulfonic acid (0.074 g) in benzene (53 mL) was heated at reflux for 20 h; water was removed in a Dean-Stark apparatus. Diethyl ether was added to the resulting mixture, and the organic layer was washed with water and brine, followed by drying over anhydrous $MgSO_4$, filtration, and evaporation. The obtained residue was purified by silica-gel column chromatography (hexanes-ethyl acetate-Et_3N, 9:0.9:0.1), to give compound **16** (1.85 g, 8.08 mmol, 60%) as a white solid (mp 37–38 ºC).

^{1}H NMR (500 MHz, $CDCl_3$): δ 4.03 (m, 2 H), 4.11 (m, 2 H), 5.75 (s, 1 H), 7.35 (d, 2 H, *J* = 8.2 Hz), 7.51 (d, 2 H, *J* = 8.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 65.3, 103.5, 123.0, 127.5, 128.4, 136.3. HRMS *m/z* calcd. for $C_9H_9O_2Br^+$ $[M+H]^+$: 228.9864, found: 228.9776.

[4-(1,3-Dioxolan-2-yl)phenyl]{3-methoxy-4-[(triisopropylsilyl)oxy]phenyl} methanol (17)

Anhydrous tetrahydrofuran (THF, 20 mL) and a solution of *n*-butyllithium 1.3 mol/L in THF (3.93 mmol, 3.0 mL) was added to a solution of compound **16** (0.60 g, 2.62 mmol) under dry nitrogen atmosphere at −78 ºC. The mixture was stirred, and then a solution of compound **14** (0.81 g, 2.62 mmol) in 20 mL of anhydrous THF was added. The reaction mixture was stirred for 2 h at −78 ºC and kept overnight at room temperature. After this period, the reaction mixture was diluted with water and diethyl ether, and the organic layer was separated and washed with water and brine. This layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated. The obtained orange oil was purified by silica-gel column chromatography (hexanes/ethyl acetate/Et_3N, 7:2.9:0.1), to give compound **17** (0.52 g, 1.13 mmol, 43%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09 (d, 18 H, *J* = 7.1 Hz, TiPS), 1.25 (hept, 3 H, *J* = 7.1 Hz, TiPS), 2.24 (sl, 1 H), 3.76 (s, 3 H), 4.09 (m, 4 H), 5.77 (s, 1 H), 5.80 (s, 1 H), 6.73 (dd, 1 H, *J* = 8.1 Hz, *J* = 2.0 Hz), 6.81 (d, 1 H, *J* = 8,1 Hz), 6.85 (d, 1 H, *J* = 2,0 Hz), 7.37 (d, 2 H, *J* = 8,3 Hz), 7.44 (d, 2 H, *J* = 8,3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9, 17.9, 55.5, 65.3, 75.8, 103.6, 110.7, 119.1, 120.1, 126.4, 126.5, 136.8, 137.0, 145.0, 145.1, 150.9. HRMS *m/z* calcd. for $C_{26}H_{38}O_5SiNa^+$ $[M+Na]^+$: 481.2386, found: 481.2377.

Triisopropyl[2-methoxy-4-(4-methylbenzyl) phenoxy]silane (18)

The catalyst 10% palladium on activated carbon powder (0.8 mg) was added to a solution of compound **17** (0.081 g, 0.18 mmol) in a mixture of ethyl acetate/acetic acid (90:10 v/v) (about 5.0–8.0 mL or the necessary volume to dissolve all reactants). The suspension was stirred under hydrogen pressure (4 atm) at room temperature, in a stainless steel reactor. After 12 h, the catalyst was removed by filtration through Celite® and silica gel. Then, the reaction mixture was neutralized with saturated $NaHCO_3$ solution. The organic layer was separated, dried with anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The crude residue was purified by silica-gel column chromatography (hexanes-ethyl acetate, 8:2), to yield compound **18** (0.034 g, 0.088 mmol, 50%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.10 (d, 18 H, *J*

= 6.7 Hz, TiPS), 1.25 (hept, 3 H, *J* = 6.7 Hz, TiPS), 2.32 (s, 3 H), 3.75 (s, 3 H), 3.88 (s, 2 H), 6.60 (dd, 1 H, *J* = 7.9 Hz, *J* = 1.8 Hz), 6.66 (d, 1 H, *J* = 1.8 Hz), 6.78 (d, 1 H, *J* = 7.9 Hz), 7.05 (d, 2 H, *J* = 8.2 Hz), 7.09 (d, 2 H, *J* = 8.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9, 17.9, 21.0, 41.1, 55.5, 113.1, 120.2, 121.0, 128.9, 129.0, 134.3, 135.4, 138.5, 143.7, 150.7.

2-Methoxy-4-(4-methylbenzyl)phenol (19)

Tetra-*n*-butyl-ammonium fluoride 1.0 mol/L in THF (0.8 mL) was added to compound **18** (0.034 g, 0.088 mmol), to promote instantaneous cleavage of the silicon group. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The pure product was obtained as a yellow oil without further purification (0.020 g, 0.087 mmol, 98%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.32 (s, 3 H), 3.83 (s, 3 H), 3.88 (s, 2 H), 6.68 (s, 1 H), 6.69 (dd, 1 H, *J* = 8.2 Hz, *J* = 1.6 Hz), 6.84 (d, 1 H, *J* = 8.2 Hz), 7.07 (d, 2 H, *J* = 8.4 Hz), 7.11 (d, 2 H, *J* = 8.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.0, 41.1, 55.9, 111.4, 114.2, 121.6, 128.6, 129.1, 133.3, 135.5, 138.4, 143.9, 146.5. HRMS *m/z* calcd. for $C_{15}H_{17}O_2^+$ $[M+H]^+$: 229.1229, found: 229.1218.

4-(4-Hydroxy-3-methoxybenzoyl)benzaldehyde (20)

***1. Oxidation Reaction*:** Compound **17** (0.092 g, 0.20 mmol), pyridinium dichromate (0.49 g, 1.3 mmol), activated 3-Å molecular sieve (0.80 g), and dichloromethane (5 mL) were added to a round-bottom flask, under dry nitrogen atmosphere. The mixture was stirred at room temperature for 2 h, followed by filtration in sintered glass funnel using Celite®. The obtained solution was washed with water and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered, and the solvent evaporated. The obtained residue was purified by silica-gel column chromatography (hexanes-ethyl acetate-Et_3N, 7:2.9:0.1) to give the corresponding ketone protected with TiPS (triisopropylsilane) (0.075 g, 0.18 mmol, 90%).

Spectral data of ketone: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (d, 18 H, *J* = 7.2 Hz, TiPS), 1.19 (hept, 3 H, *J* = 7.1 Hz, TiPS), 3.78 (s, 3 H), 4.05 (m, 4 H), 5.82 (s, 1 H), 6.81 (d, 1 H, *J* = 8.3 Hz), 7.19 (dd, 1 H, *J* = 2.0 Hz, *J* = 8.3 Hz), 7.38 (d, 1 H, *J* = 2.0 Hz), 7.52 (d, 2 H, *J* = 8.1 Hz), 7.70 (d, 2 H, *J* = 8.1 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 12.9, 17.8, 55.5, 65.4, 103.1, 113.1, 119.4, 125.2, 126.2, 129.8, 130.6, 141.5, 150.3, 150.9, 195.3.

***2. Cleavage of the protection*:** The obtained ketone (0.050 g, 0.12 mmol) was dissolved in 2 mL of THF and a solution of tetra-*n*-butyl-ammonium fluoride in THF (0.50 mL, 1.0 mol/L) was added, to promote instantaneous cleavage of the silyl group. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated. The obtained crude residue was dissolved in 2 mL of methanol, drops of concentrated HCl (5 mL) were added, and the mixture was stirred at room temperature, for 3 h. Methanol was evaporated under reduced pressure, and the resulting residue was diluted in ethyl acetate and washed with water and brine. The organic layer was separated, dried over anhydrous $MgSO_4$, and filtered, and the solvent was evaporated. The obtained residue was purified by silica-gel column chromatography (hexanes-ethyl acetate, 8:2) to give compound **20** (0.028 g, 0.11 mmol, 91%) as a yellow solid (mp 111–112 ºC).

Compound 20: ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.26 (s, 1 H), 3.99 (s, 3 H), 6.97 (d, 1 H, *J* = 8.1 Hz), 7.29 (dd, 1 H, *J* = 1.6 Hz, *J* = 8.1 Hz), 7.53 (d, 1 H, *J* = 1.6 Hz), 7.87 (d, 2 H, *J* = 8.1 Hz), 8.00 (d, 2 H, *J* = 8.1 Hz), 10.1 (s, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.1, 111.5, 113.8, 126.5, 129.0, 129.4, 129.9, 138.0, 143.5, 146.9, 150.9, 191.7, 194.6. HRMS *m/z* calcd. for $C_{15}H_{13}O_4^+$ $[M+H]^+$: 257.0814, found: 257.0808.

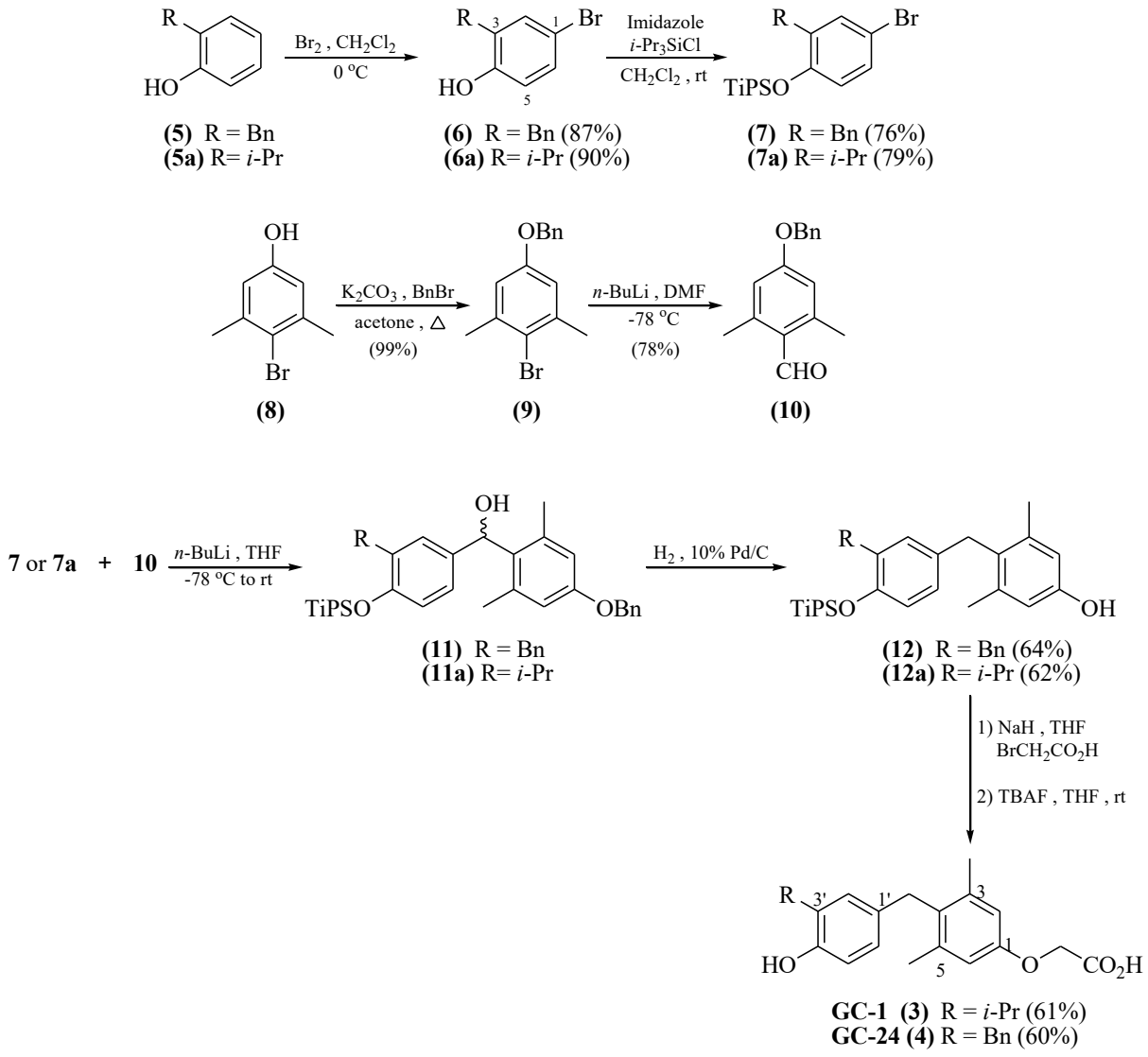
3. RESULTS AND DISCUSSION

According to Scheme 1, the synthetic route described here allowed preparation of the two target compounds: **GC-1** (**3**) and **GC-24** (**4**). Starting with 2-hydroxydiphenylmethane (**5**) and/or 2-isopropylphenol (**5a**), the bromination reaction in the *para*-position to the hydroxyl group yielded the corresponding brominated compounds **6** and/or **6a** (87% and 90% yields, respectively) after purification by silica-gel column chromatography. Treatment of the resulting products with triisopropylsilyl chloride furnished the bromo-arylsilyl ethers **7** and **7a** (76% and 79% yields, respectively). Protection of the commercially available compound 4-bromo-3,5-dimethylphenol (**8**) as the benzyl ether **9** (99% yield),

followed by a formylation reaction via lithium-halogen exchange and addition of dimethylformamide afforded the benzaldehyde derivative **10** (78% yield).

The bromide compound **7** and **7a** and the aldehyde **10** were coupled, to produce the biaryl alcohol **11** and **11a**, which were used in the following steps without further purification. Hydrogenolysis of the crude alcohol **11** and **11a** promoted the simultaneous cleavage of the hydroxyl and benzyl groups, furnishing the biarylmethane compound **12** and **12a** (64% and 62% yields, respectively). The reaction to insert the acid group in compounds **12**/**12a** was performed with bromoacetic acid, using NaH as base, under reflux in THF. A one-pot procedure with TBAF deprotected the silyl ether group of the obtained crude products, directly producing the target compounds **GC-1** (**3**) and **GC-24** (**4**). The latter compounds were purified by silica-gel column chromatography; a mixture of hexanes/EtOAc (6:4) containing small amount of acetic acid (2% in volume) was used as eluent. This procedure yielded the ligands **GC-1** (**3**) and **GC-24** (**4**) as pure solids from compounds **12a** and **12**, respectively; yields were 61% and 60%, respectively. The overall yields for the synthesis of six steps of the **GC-1** (**3**) and **GC-24** (**4**) ligands from the commercially available 4-bromo-3,5-dimethylphenol (**8**) were 29% and 30%, respectively.

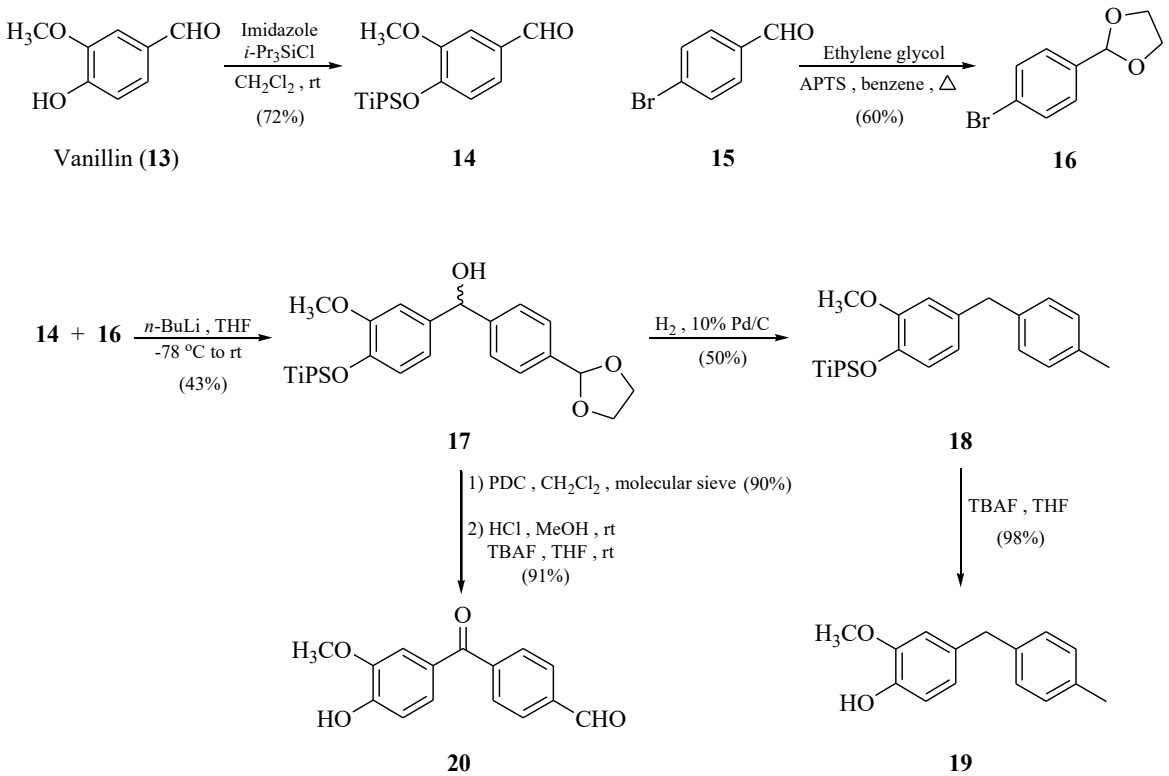
1D NMR (^{1}H and ^{13}C) and 2D NMR (^{1}H–^{13}C correlation) spectroscopic analyses using deuterated methanol as solvent helped to elucidate the structures of the synthesized **GC-1** (**3**) and **GC-24** (**4**). The spectral data of **GC-1** (**3**) were equivalent to those previously described in the literature [13].



Scheme 1. Synthetic route used to prepare the TR ligands **GC-1** (**3**) and **GC-24** (**4**).

Scheme 2 shows the synthetic route that we employed to prepare the new ligands **18** and **19**. Compound **19** displays a very interesting structure: it bears an aldehyde group in position 1 and a ketone group between two aromatic rings. First, treatment of commercial vanillin (**13**) with triisopropylsilyl chloride provided compound **14** (72% yield). Next, the commercially available compound *p*-bromobenzaldehyde (**15**) was protected as a diethyl acetal compound (**16**) (60% yield). Purification of compound **16** by silica gel column chromatography was very difficult, because acid silica readily removed the protective group. This calls for addition of a basic reagent (e.g., triethylamine) to the silica gel, to prevent hydrolysis of the acetal group.

Coupling of compounds **14** and **16** gave the biaryl alcohol **17** (43% yield), later submitted to a hydrogenolysis reaction under acid condition. The experimental condition promoted simultaneous cleavage of both hydroxyl and acetal groups of compound **17**, to produce the biarylmethane compound **18** (50% yield). Subsequent treatment of **18** with tetrabutylammonium fluoride removed the silyl ether protecting group and almost instantaneously generated compound **19** (98% yield) as a new TR ligand. Submission of compound **17** to an oxidation reaction with pyridinium dichromate (PDC) in dichloromethane and subsequent removal of the acetal and silyl groups afforded the new ligand **20**. The overall yields for the synthesis of ligands **19** (four steps) and **20** (four steps) from compound **15** were 13% and 21%, respectively. The successful preparation of the novel ligands **19** and **20** motivates the continuous development of new ligands with greater therapeutic value.



Scheme 2. Synthetic route used to prepare the novel ligands **19** and **20**.

4. CONCLUSION

We have developed a useful route to synthesize the ligands GC-1 (3) and GC-24 (4). This new synthetic route allows preparation of the ligands in fewer steps and improves the overall yield as compared with the original synthesis of GC-1 (3) described in the literature. We have also developed the synthesis of two novel analogues of THs by a new and efficient synthetic route. The developed synthetic routes enable selective modification of the original thyronine skeleton, to produce new and useful derivatives. Our research group is now performing structural and functional studies of the synthetic compounds associated with specific proteins by

crystallographic analysis [23-25].

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6. REFERENCES AND NOTES

[1] Barra, G. B.; Velasco, L. F. R.; Pessanha, R. P.; Campos, A. M.; Moura, F. N.; Dias, S. M. G.; Polikarpov, I.; Ribeiro, R. C. J.; Simeoni, L. A.; Neves, F. A. R. *Arq. Bras. Endocrinol. Metab.* **2004**, *48*, 25. [CrossRef]

[2] Nguyen, N-H.; Apriletti, J. W.; Baxter, J. D.; Scanlan, T. S. *J. Am. Chem. Soc.* **2005**, *127*, 4599. [CrossRef]

[3] Burris, T. P.; Solt, L. A.; Wang, Y.; Crumbley, C.; Banerjee, S.; Griffett, K.; Lundasen, T.; Hughes, T.; Kojetin, D. J. *Pharmacol. Rev.* **2013**, *65*, 710. [CrossRef]

[4] Loireau, A.; Autissier, N.; Dumas, P.; Michael, O.; Jorgensen, E. C.; Michael, R. *Biochem. Pharmacol.* **1986**, *35*, 1691. [CrossRef]

[5] Engelken, S. F.; Eaton, R. P. *Atherosclerosis* **1981**, *38*, 177. [CrossRef]

[6] Hansson, P.; Valdemarsson, S.; Nilsson-Ehle, P. *Horm. Metab. Res.* **1983**, *15*, 449. [CrossRef]

[7] Scarabottolo, L.; Trezzi, E.; Roma, P.; Catapano, A. L. *Atherosclerosis* **1986**, *59*, 329. [CrossRef]

[8] Bassett, J. H. D.; O'Shea, P. J.; Sriskantharajah, S.; Rabier, B.; Boyde, A.; Howell, P. G. T.; Weiss, R. E.; Roux, J. P.; Malaval, L.; Clement-Lacroix, P. *Mol. Endocrinol.* **2007**, *21*, 1095. [CrossRef]

[9] Sun, L.; Liu, X.; Zhu, L. L.; Liu, J. H.; Liu, Q. C.; Iqbal, J.; Mechanick, J.; Davies, T.; Zaidi, M. *Clinic. Rev. Bone Miner. Metab.* **2008**, *6*, 95. [CrossRef]

[10] Ye, L.; Li, Y. L.; Mellstrom, K.; Mellin, C.; Bladh, L. G.; Koehler, K.; Garg, N.; Garcia Collazo, A. M.; Litten, C.; Husman, B.; Persson, K.; Ljunggren, J.; Grover, G.; Sleph, P. G.; George, R.; Malm, J. *J. Med. Chem.* **2003**, *46*, 1580. [CrossRef]

[11] Trost, S. U.; Swanson, E.; Gloss, B.; Wang-Iverson, D. B.; Zhang, H.; Volodarsky, T; Grover, G. J.; Baxter, J. D.; Chiellini, G.; Scanlan, T. S.; Dillmann, W. H. *Endocrinology* **2000**, *141*, 3057. [CrossRef]

[12] Wikstrom, L.; Johansson, C.; Salto, C.; Barlow, C.; Barros, A. C.; Baas, F.; Forrest, D.; Thoren, P.; Vennstrom, B. *EMBO J.* **1998**, *17*, 455. [CrossRef]

[13] Chiellini, G.; Nguyen, N. H.; Yoshihara, H. A. I; Scanlan, T. S. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2607. [CrossRef]

[14] Chiellini, G.; Apriletti, J. W.; Yoshihara, H. A.; Baxter, J. D.; Ribeiro, R. C. J.; Scanlan, T. S. *Chem. Biol.* **1998**, *5*, 299. [CrossRef]

[15] Scanlan, T. S. *Heart Fail Rev.* **2010**, *15*, 177. [CrossRef]

[16] Grover, G. J.; Egan, D. M.; Sleph, P. G.; Beehler, B. C.; Chiellini, G.; Nguyen, N-H.; Baxter, J. D.; Scanlan, T. S. *Endocrinology* **2004**, *145*, 1656. [CrossRef]

[17] Borngraeber, S.; Budny, M-J.; Chiellini, G.; Cunha-Lima, S. T.; Togashi, M.; Webb, P.; Baxter, J. D.; Scanlan, T. S.; Fletterick, R. J. *Proc. Natl. Acad. Sci. USA.* **2003**, *100*, 15358. [Crossref]

[18] Amorim, B. S.; Ueta, C. B.; Freitas, B. C.; Nassif, R. J.; Gouveia, C. H.; Christoffolete, M. A.; Moriscot, A. S.; Lancelloti, C. L.; Llimona, F.; Barbeiro, H. V.; De Souza, H. P.; Catanozi, S.; Passarelli, M.; Aoki, M. S.; Bianco, A. C.; Ribeiro, M. O. *J. Endocrinol.* **2009**, *203*, 291. [CrossRef]

[19] Miyabara, E. H.; Aoki, M. S.; Soares, A. G.; Saltao, R. M.; Vilicev, C. M.; Passarelli, M.; Scanlan, T. S.; Gouveia, C. H.; Moriscot, A. S. *Cell Tissue Res.* **2005**, *321*, 233. [CrossRef]

[20] Ocasio, C. A.; Scanlan, T. S. *Curr. Opin. Endocrinol. Diabetes* **2005**, *12*, 363. [CrossRef]

[21] Baxter, J. D.; Webb, P. *Nat. Rev. Drug Discov.* **2009**, *8*, 308. [CrossRef]

[22] Davis, P. J.; Mousa, S. A.; Cody, V.; Tang, H. Y.; Lin, H. Y. *Horm. Canc.* **2013**, *4*, 335. [CrossRef]

[23] Trivella, D. B. B.; Sairre, M. I.; Foguel, D.; Lima, L. M. T. R.; Polikarpov, I. *J. Struct. Biol.* **2011**, *173*, 323. [CrossRef]

[24] Martinez, L.; Polikarpov, I.; Skaf, M. S. *J. Phys. Chem. B.* **2008**, *112*, 10741. [CrossRef]

[25] Valadares, N. F.; Polikarpov, I.; Garrat, R. C. *J. Steroid Biochem. Mol. Biol.* **2008**, *112*, 205. http://dx.doi.org/10.1016/j.jsbmb.2008.10.006